(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 283 140
A3

(12) EUROPEAN PATENT APPLICATION

(21) Application number: 88301475.5

(22) Date of filing: 22.02.88

(51) Int. Cl.⁴: A 61 K 31/20

(30) Priority: 09.03.87 GB 8705459

(43) Date of publication of application:
21.09.88 Bulletin 88/38

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(88) Date of deferred publication of search report:
26.07.89 Bulletin 89/30

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(54) Compositions and method for treatment of peptic ulcers.

(57) Treatment or prevention of occurrence or reoccurrence of peptic ulcers by administering to a person suffering or at risk of suffering from the same, 1mg to 50g per day, advantageously 10mg to 1g per day, of one or more essential fatty acids selected from the 18:3 and higher acids of the n-6 series and the 18:4 and higher acids of the n-3 series.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number

EP 88 30 1475

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int Cl 4)
X,Y	EP-A-0 195 570 (EFAMOL LTD.)		A 61 K 31/20
	* Column 1, line 15 - column 2, line 13; column 2, line 14 - column 4, line 66; column 9, line 51 - column 10, line 30, claims *	1-3	
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X	EP-A-0 101 294 (EFAMOL LTD.)		
	* Page 2 ,line 6 - page 3, line 24; claims *	1-3	
	--		
X	GUT, vol. 27, 1986, pages 239-242; D. HOLLANDER et al.: "Dietary essential fatty acids and the decline in peptic ulcer disease - a hypothesis"		
	* Whole document *	1-3	
	--		TECHNICAL FIELDS SEARCHED (Int Cl 4)
X	J. LAB. CLIN. MED. vol. 102, 1983, pages 340-351		A 61 K
	./.		

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely: 1-3

Claims searched incompletely:

Claims not searched: 4-6

Reason for the limitation of the search:

Method for treatment of the human or animal body by surgery or therapy (See art. 52(4) of the European Patent Convention)

TO BE RELEVANT		CLASSIFICATION OF THE APPLICATION (Int Cl 4)
e appropriate, of relevant	Relevant to claim	
"Arachidonic stric mucosa y: sequential ic and funct-		
page 341, 349-350 *	1-3	
l. 100,		
"Arachidonic t gastric l injury"		TECHNICAL FIELDS SEARCHED (Int Cl 4)
section "re- first section 'discussion" -	1-3	
OL. vol. 22, ; pages		
"Cytoprotec- essential lfate"		
1 *	1-3	
OL., vol. 20 ges 41-48 'Protection mucosa by		
ection "Intro- left-hand page 44, line 15 - column, ft-hand co- e 46, right-] *	1-3	
1; 1987		
e role of bolites in stasis"		

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int Cl 4)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	* Summary; page 41, left-hand column, line 19 - page 42, right-hand column, line 2 *	1-3	
	---		TECHNICAL FIELDS SEARCHED (Int Cl 4)

ETHOD FOR TREATMENT OF PEPTIC ULCERS

ons and methods for the treatment or prevention of occurrence or

OUND

first is that considerable interest has been shown in recent years in
s in medicine.
levels of prostaglandins are required it is not usually practical to
ndins such as PGE1 and PGE2 to patients. Consequently consider-
of prostaglandin precursors including linolenic acid, gamma-linoleic
acid (DGLA).
body is believed to be as shown in the following diagram:-

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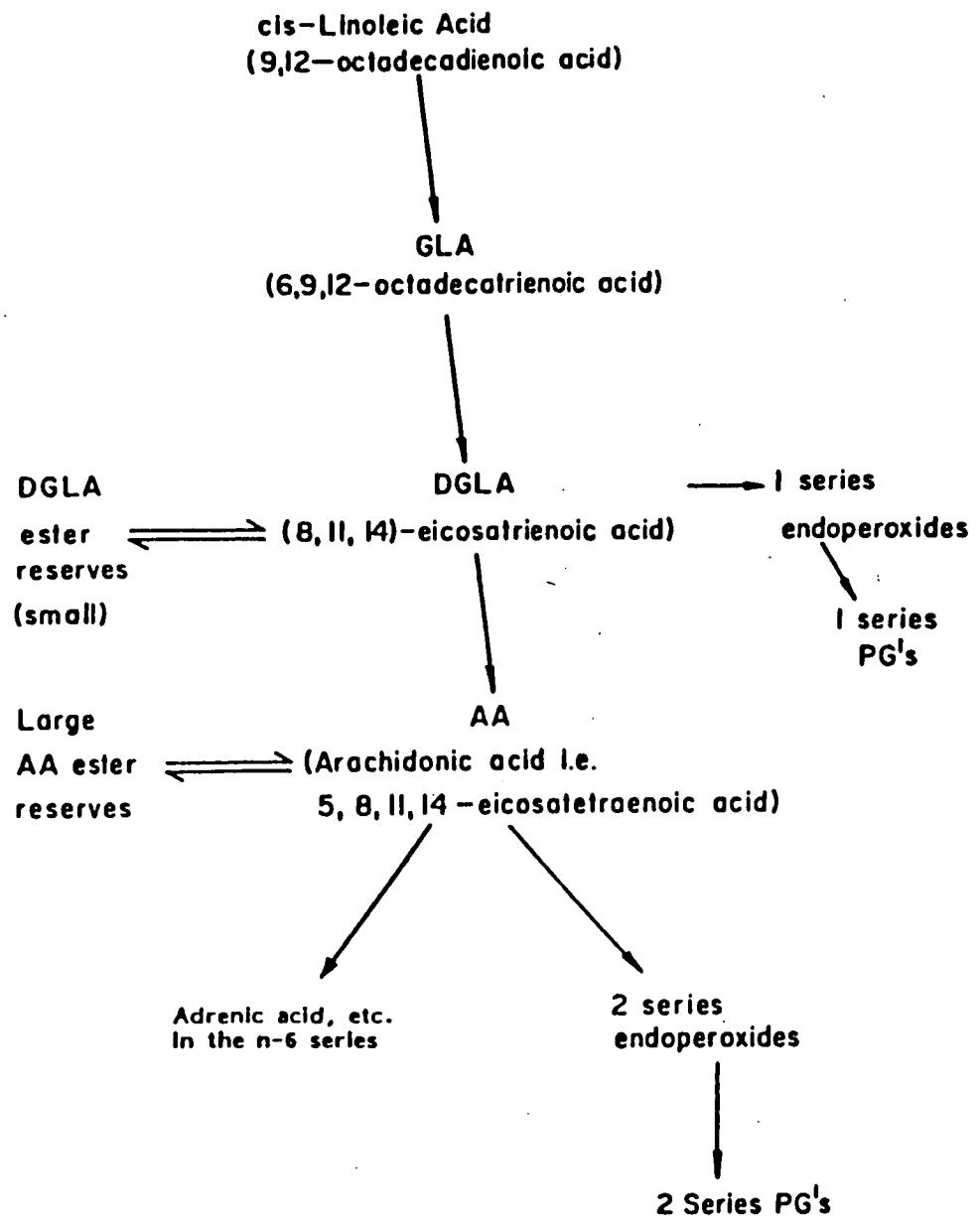

The broad out of this pathway is well known, and it brings out clearly that a major function of essential fatty acids (EFAs) is to act as precursors for prostaglandins. 1-series PGs being formed from

gamma-linolenic acid (GLA) and then to DGLA and AA, the latter step being irreversible. The conversion of linoleic acid to GLA is a limiting step, adequate in the young and healthy body but often inadequate in ageing or in many diseased states.

DGLA is the key substance. GLA is almost completely and very rapidly converted in the body to DGLA and so for practical purposes the oral administration of DGLA and GLA amounts to the same thing. DGLA can be converted to a storage form, changed to arachidonic acid and thence to PGs of the 2-series, or converted to PGs of the 1-series.

The second part of the background is increasing awareness of the significance of the essential fatty acids in themselves, in which considerable general interest has been shown in recent years, primarily in the acids of the n-6 series both as such and in relation to prostaglandin metabolism but also in the acids of the n-3 series. The n-6 acids in particular are required in the body for the structure of membranes in and around cells, being believed to be necessary for maintaining normal flexibility, fluidity and permeability of such membranes, and while less is known of the role of the n-3 series acids they are equally present.

The pathways of metabolism of the n-6 essential fatty acids and the related n-3 acids sharing, it is believed, common enzymes in the two pathways, are:-

n-6	n-3
18:2 delta-9,12 (linoleic acid)	18:3 delta-9,12,15 (alpha-linolenic acid)
↓ delta-6 desaturase	↓
18:3 delta-6,9,12 (gamma-linolenic acid)	18:4 delta 6,9,12,15
↓ elongation	↓
20:3 delta 8,11,14 (dihomo-gamma-linolenic acid)	20:4 delta-8,11,14,17
↓ delta-5 desaturase	↓
20:4 delta-5,8,11,14 (arachidonic acid)	20:5 delta 5,8,11,14,17
↓ elongation	↓
22:4 delta-7,10,13,16 (adrenic acid)	22:5 delta-7,10,13,16,19
↓ delta-4 desaturase	↓
22:5 delta-4,7,10,13,16	22:6 delta-4,7,10,13,16,19

The pathways are not normally reversible nor in m

The acids, which naturally are of the all-cis configu corresponding octadecanoic, eicosanoic or docosanoic 4,7,10,13,16,19-docosahexaenoic acid, but numerical d n-3 is convenient initials, for example, DHA for 22:6 n- serve when n-3 and n-6 acids of the same chain lengt more or less common use in the n-6 series are as sho used trivial name, alpha-linolenic acid. It was characte in the literature simply to linolenic acid, especially in the

In the body, the n-3 acids are metabolised prefere of alpha-linolenic acid (18:3 n-3) are low and 18:4 n-3 the n-6 acids are normally present in moderate amo levels, being apparently converted to dihomo-gamma-l slow production from linoleic acid. In both series the el more rapid that the desaturations.

SPECIFIC BACKGROUND

Peptic ulcers of the stomach and duodenum are v diet or by several different drugs. The two most effec antagonists and the prostaglandin (PG) analogues. Th histamine and so reducing acid secretion. The PG anal part by increasing the defences of the gastroduodenal process which has been termed "cytoprotection".

Patients whose ulcers have been healed by one susceptible to a recurrence of peptic ulceration. This re but there is a reluctance on the parts of both doctors risk of adverse effects. There is therefore a need to against long term ulcer recurrence.

One possible approach would be to increase the mucosa. If PGs are indeed cytoprotective, this would e to be increased. One limited way of doing this might b Gammalinolenic acid (GLA) to dihomo-gamma-linolenic of potentially cytoprotective prostaglandins. Unfortunat high cholesterol levels and diabetes are known to red that, especially in adult humans following lifestyles kn gastro-duodenal PG production is inadequate. The blo provision of GLA, DGLA, or AA. GLA is rapidly conv produce PGs from the DGLA and AA precursors.

In tests in normal individuals we have shown that primrose oil can indeed raise gastric PG levels significa even in the presence of aspirin which is known to inhibi PG levels and those stimulated by evening primrose oil with the drop present GLA was able to produce a signifi

PG synthesis from DGLA and AA can be inhibited such as eicosapentaenoic acid (EPA) and docosahexae PG synthesis by competing with DGLA or AA for the cy feeding EPA and DHA to people would reduce PG s gastric mucosa to damage.

One measure of such susceptibility is to administ gastro-duodenal mucosa enough to cause small amount the loss of blood in the faeces. We therefore administ individuals and compared the blood loss. To our significantly reduce administering the fish oil, which

...d acids may be able to protect the gastro-duodenal mucosa in
...t at least act by some quite different mechanism which is
...that the administration of such polyunsaturated fatty acids,
...ner alone or in combination as having therapeutic value in the
...are known to be very safe in long term administration at the
...advantages over other available techniques. Other possible
...22.4 n-6, 22.5 n-6, 18.4 n-3, 20.4 n-3, 22.5 n-3. The parent
...c acid are unlikely to be of value except at unrealistic dose
...uration.
...in the use of one or more essential fatty acids selected from
...he 18.4 and higher n-3 series acids for the preparation of
...of occurrence or reoccurrence of peptic ulcers by administra-
...0 1g per day, of said acids.
...3, 20.3, 20:4, 22.4, 22.5, acids of the n-6 series and the 18.4
...s.
...the method of treatment or prevention of peptic ulcers
...ch purposes in such amounts.

...pharmaceutically acceptable and physiologically equivalent
...gamma-linolenic acid and dihomo-gamma-linolenic acid, and
...s including reference to the acids when in the form of such
...free acids. Equivalence is demonstrated by entry into the
...cts corresponding to those of the acids themselves or their
...ication of useful derivatives is by their having the valuable
...sion can be shown directly by gas chromatographic analysis
...ssue by standard techniques, for example those of Pelick et
...s" Ed. Perkins, American Oil Chemist Society, Champaign,

...atives of gamma-linolenic acid and dihomo-gamma-linolenic
...yceride esters and alkyl (eg. C1 to C4) esters, alcohols and

...ay be produced for use in the invention by associating the
...rivatives, with an acceptable pharmaceutical vehicle. It is,
...at least the gamma-linolenic acid into compositions in the
...olenic acid content, hence references to "oil" herein
...or oils having a high gamma-linolenic acid content are few
...nt amounts of dihomo-gamma-linolenic acid). One source of
...g Primrose species such as **Oenothera biennis** L. and
...om containing gamma-linolenic acid (about 8%) and linoleic
...together with other glycerides (percentages based on total
...acid are Borage species such as **Borago officinalis** which,
...richer source of gamma-linolenic acid than Oenothera oil.
...by fermentation promise a fungal oil source.
...e of the conventional methods of extraction such as cold
...the seed, or solvent extraction.
...the form of methyl esters shows the relative proportions.

...an be used as such or can, for example, if desired, be
...ing the triglycerides of gamma-linolenic and linoleic as the

...acid components, the gamma-linolenic and linoleic as the main fatty acid components, the
...lenic acid content being if desired a major proportion. Seed oil extracts appear to have a
stabilising effect upon dihomo-gamma-linolenic acid if present.

Natural sources of 22:4 and 22.5 n-6 acids include adrenal glands (22.5) and kidneys (22:4) obtained from slaughter houses, and 22:4 in the fat of the American Snapping Turtle. The n-3 acids are available from fish oils, particularly 20:5 n-3 and 22.6 n-3. The acids can be isolated from these sources by, for example, saponification under mild non-oxidising conditions followed by preparative gas liquid chromatography. Synthesis of the acids is difficult but not impossible and provides another source.

Advantageously, a preservative is incorporated into the preparations: alpha-tocopherol in concentration of about 0.1% by weight has been found suitable for the purpose.

EXAMPLES

The following are examples of medicaments produced according to the invention and their administration according to the method of the invention, as soft or hard gelatine capsules produced by per se conventional methods and suited to oral administration as the most convenient method of delivering the active compounds to the stomach and duodenum. Other method of administration leading to enhanced levels therein are, however, not excluded.

1. Capsules containing 1g fish oil comprising 25% EPA and 7% DHA by weight, 8 per day.
2. Capsule containing 500mg evening primrose oil comprising 9% GLA by weight, 12 per day
3. Capsules containing 2g of a mixture of the fish oil from 1. and the evening primrose oil form 2. in equal proportions by weight, 6 per day.
4. Capsules containing 200mg ethyl-EPA, 200mg ethyl-DHA, 200mg ethyl-AA and 200mg ethyl-DGLA, 6 per day.
5. In a bland diluent, an EPA concentrate containing by weight 60% EPA and 15% DHA, 6g per day of the concentrate.

Similarly:-

6. 5g/day of pure GLA
7. 10g day of pure EPA
8. 2g day of pure DHA
9. 1g day of pure AA
10. 4g day of pure DGLA
11. Capsules containing 200mg EPA, 100mg GLA and 50mg each of DGLA, AA, DHA, 22.4 n-6, 22.5 n-6, 18.4 n-3 and 20.4 n-3, 4 per day

Claims

1. The use of one or more essential fatty acids selected from the 18:3 and higher acids of the n-6 series and the 18.4 and higher acids of the n-3 series, for the preparation of medicaments for the treatment or prevention of occurrence or reoccurrence of peptic ulcers by administration of 1mg to 50g per day, advantageously 10mg to 1gm per day, of said acids.
2. The use of essential fatty acids selected from the 18:3, 20.3, 20:4, 22:4 and 22.5 acids of the n-6 series and the 18.4, 20:4, 20:5, 22.5 and 22.6 acids of the n-3 series as in claim 1.
3. The use according to claim 1 or 2, wherein the said acids are in the form of their salts, amides, esters, alcohols, phospholipids or pharmaceutically acceptable and physiologically equivalent derivatives.
4. Treatment or prevention of occurrence or reoccurrence of peptic ulcers by administering to a person suffering or at risk of suffering from the same, 1mg to 50g per day, advantageously 10mg to 1g per day of one or more essential fatty acids selected from the 18.3 and higher acids of the n-6 series and the 18.4 and higher acids of the n-3 series.
5. Treatment according to claim 4, wherein the acids administered are essential fatty acids selected from the 18:3, 20:3, 20.4, 22:4 and 22.5 acids of the n-6 series and the 18.4, 20.4, 20:5, 22.5 and 22.6 acids of the n-3 series.
6. Treatment according to claim 4 or 5, wherein the said acids are in the form of their salts, amides esters, alcohols, phospholipids or pharmaceutically acceptable and physiologically equivalent derivatives